RESPONSE

I. Status of the Claims

Prior to the third Action, claims 4-9, 23-27, 41 and 49-83 were pending and have been examined. Presently, claims 4-6, 24, 55, 56, 59, 60, 65 and 68-82 have been amended without prejudice or disclaimer. Claims 84-88 have been added, which are fully supported by the application as filed and unified with the examined claims. No claims have been cancelled.

Claims 4-9, 23-27, 41 and 49-88 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section. Double-brackets are used instead of strikeout for clarity in amended claims 55, 56 and 59.

II. Date of Third Action

The third Action, originally mailed on October 20, 2005, included a number of rejections under 35 U.S.C. § 103(a) that relied on Holash, a post-filing date reference, although Holash was not recited in the formulation of such § 103 rejections. Applicants appreciate the Office re-mailing the third Action to correct this matter (Action re-mailed on November 16, 2005).

III. Applicants' Interview Summary

Applicants' agree with the Interview Summary attached to the third Action mailed on November 16, 2005. However, Applicants also pointed out during the interview that a post-filing date reference cannot be used as a critical part of a combination of references in a rejection under 35 U.S.C. § 103(a), and that the attempt to use Holash in the present § 103(a) rejections was particularly improper for scientific reasons.

IV. Prosecution History and Rejections Overcome

In the first Action, each of claims 5, 8-10, 23-26, 41, 57, 58, 61, 62, 64 and 65 were found to be allowable. Many of those allowable claims were placed into independent form in

Applicants' first response. The second Action entered non-final rejections against most of the formerly allowable claims, but indicated claims 23-26 and 72-74 to be allowed or allowable.

Although withdrawing the last rejection under 35 U.S.C. § 103(a) (U.S. Patent No. 6,300,308 to Schroit in combination with U.S. Patent No. 5,725,856 to Hudziak), the third Action has now entered a number of new non-final rejections against all claims. Despite these non-final rejections, the present response and accompanying documents show that all pending claims are in condition for allowance.

V. Support for the Claims

Support for the revised and new claims is to be found throughout the specification and claims of the original and parent applications. Should any small entity fees be necessary for the new dependent claims, such fees should be deducted from Peregrine Pharmaceuticals, Inc. Deposit Account No. 50-3493/4001.002299.

Claim 4 has been amended to recite that the first antibody, or antigen-binding fragment thereof, "targets and" binds to "an aminophospholipid-protein complex" on the luminal surface of blood vessels of the vascularized tumor. These embodiments are supported in the original and parent specifications, *e.g.*, in the present specification at least at pages 2 and 6-16, particularly at page 2, line 15; page 4, line 30; page 5, lines 10 and 17; page 6, line 30; page 7, lines 1, 2, 7, 14, 16, 19, 21, 23 and 25; page 8, lines 2 and 3; page 16, line 15; page 21, lines 1, 2, 5, 12, 13 and 15; and page 22, line 26 (targeting) and at page 7, lines 3-4 and page 7, lines 25-30 (complex). H_2O_2, thrombin and calcium flux inducing agent have also been removed from the recited second therapeutic agents.

Claims 5, 6 and 24 have been amended to refer to phosphatidylethanolamine protein complexes, phosphatidylserine-protein complexes and aminophospholipid-protein complexes,

respectively, which are consistent with claim 4 and supported by the specification as exemplified above.

Claims 55, 56 and 59 have been amended to depend from claim 73, and claim 60 has been amended to depend from claim 59.

Claim 64 has been amended to remove calcium ionophores and calcium-flux inducing agents from the recited second therapeutic agents.

Claim 68 has been revised to be an independent claim in which the recited antibody targets and binds to a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor. Otherwise, the wording of claim 68 and the recited second therapeutic agents have been revised to match current claim 4.

Claim 69, an independent claim in which the recited antibody targets and binds to phosphatidylethanolamine, has been revised to remove the same second therapeutic agents deleted from claim 4.

Each of claims 70, 71 and 72 has been revised similarly to claim 4, *i.e.*, to recite targeting and binding to an aminophospholipid-protein complex and to remove H_2O_2, thrombin and calcium flux inducing agents.

Also, claim 72 has been revised to specify the use of a "tumor-destructive amount" of the recited anti-aminophospholipid antibody. This is supported throughout the specification as filed, *e.g.*, at least at pages 7-12, particularly page 8, line 25. See also, claims 3 and 53 issued in the parent case, U.S. Patent No. 6,406,693 ("the '693 patent"; Attorney Docket No. 4001.002200).

Claim 73 is the only independent claim that maintains H_2O_2, thrombin and calcium flux inducing agents. This claim also recites targeting and binding to an aminophospholipid-protein complex and removes intravenous administration.

Each of claims 74, 75, 76, 77, 78, 79, 80 and 81 has been revised similarly to claim 4, *i.e.*, to recite targeting and binding to an aminophospholipid-protein complex, and to remove H_2O_2, thrombin, calcium flux inducing agents and calcium ionophores, where recited.

In addition, claims 78 and 79 have been revised to specify the use of certain effective amounts of the recited anti-aminophospholipid antibodies, as supported in the specification as filed, *e.g.*, at least at pages 7-12. Claim 79 recites a "tumor necrosis-inducing amount", which is supported throughout the specification as filed, *e.g.*, at least at pages 7-12, particularly page 9, lines 6-7. See also, claims 45 and 60 in the parent, '693 patent. Claim 79 specifies the use of "an amount effective to destroy or occlude at least a portion of the tumor blood vessels", which is supported throughout the specification as filed, *e.g.*, at least at pages 7-12, particularly page 8, lines 28-30. See also, claims 2, 44, 52 and 59, and particularly claims 50 and 63, in the parent, '693 patent.

Claim 82 is the only independent claim that maintains the definition of an antibody that binds to an aminophospholipid, rather than an antibody that targets and binds to aminophospholipid-protein complex. This claim also removes H_2O_2, thrombin and calcium flux inducing agents from the second therapeutic agents.

New dependent claim 84 further limits revised claim 4 by reciting that the antibody, or antigen-binding fragment thereof, binds to a phosphatidylserine and β_2-glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor. This is also supported by the specification as set forth above for claim 4, with particular reference to page 7, lines 28 and 29.

New dependent claim 85 further limits revised claim 73 by reciting that the second therapeutic agent is administered via direct instillation into the vascularized tumor. This is

supported in the original and parent specifications, *e.g.*, in the present specification at least at page 100, line 12.

New dependent claims 86 and 87 further limit claim 82 by separately reciting an antibody that binds to phosphatidylethanolamine and phosphatidylethanolamine, respectively. These claims therefore correspond to original claims 5 and 6.

Finally, dependent claim 88 further limits claim 82 by reciting an antibody that binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor, which is supported by the specification as set forth above for claim 4.

It will therefore be understood that no new matter is included within any of the amended or new claims.

VI. First Double-Patenting Rejection

Claims 4-9, 24, 27, 41 and 49-83 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11, 17-20 and 27-54 of U.S. Patent No. 6,783,760 ("the '760 patent"; Attorney Docket No. 3999.002399). Although Applicants respectfully traverse, this rejection can be overcome by filing a terminal disclaimer if necessary to secure issuance.

The '760 patent claims certain combination treatment methods. Regarding the second therapeutic agents, Applicants note that the combination treatment method claims of the '760 patent recite administering H_2O_2 and thrombin in claim 48, and administering calcium-flux inducing agents and calcium ionophores in claims 34, 51 and 52.

As to the primary therapeutic agent, Applicants earlier pointed out that the claims of the '760 patent recite administering a therapeutic conjugate, in which a therapeutic agent is delivered

to the tumor by attachment to a targeting agent that binds to an aminophospholipid, whereas the present claims all rely on the administration of a naked or unconjugated antibody.

The third Action appears to agree with such reasoning, but contends that the pending claims do not recite "that the antibody is naked or unconjugated" (third Action at page 3). Applicants respectfully point out that, prior to the third Action, claims 68 and 82 expressly recited administering an "unconjugated antibody". Claim 69 now also includes the term "unconjugated".

As to the remaining claims, the third Action contends that Applicants are arguing limitations [unconjugated] that are not present in the pending claims (third Action at page 3). On the contrary, Applicants are using the word "antibody" according to its ordinary and customary meaning, which meaning is also expressly defined in the specification:

> "As used herein, the term 'anti-aminophospholipid antibody' is used co-extensively with 'naked and unconjugated' to mean anti-aminophospholipid antibodies, and antigen binding fragments thereof, that are not conjugated to, or operatively associated with, an effector molecule, such as a cytotoxic agent or coagulant. In addition to non-effector modifications of the antibody, and *in vivo* interactions, the term 'naked' in no way excludes combinations of the antibody with other therapeutic agents, as disclosed in detail herein."
>
> Specification at page 19, lines 12-17.

The specification thus defines "antibody" to mean "naked" and "unconjugated" antibodies, and antigen binding fragments thereof, which are not conjugated to, or operatively associated with, an effector molecule. This is in accordance with the ordinary and customary meaning of "antibody", as those of ordinary skill in the art do not use "antibody" synonymously with "immunoconjugate". Therefore, Applicants are not "arguing limitations that are not present in the pending claims", but are explaining the non-obviousness of the claims when properly interpreted.

The first obviousness-type double patenting rejection is therefore overcome and should be withdrawn. Nonetheless, if double patenting rejection(s) are the only rejections remaining in the case, Applicants will overcome the rejection(s) by filing a terminal disclaimer.

VII. Second Double-Patenting Rejection

Claims 4-9, 41, 49-51, 53, 57, 58, 61, 68-71, 75-78 and 80-83 are also rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 4-11, 28, 29 and 43 of U.S. Patent No. 6,312,694 ("the '694 patent"; Attorney Docket No. 3999.002300). Although Applicants respectfully traverse, this rejection can be overcome by filing a terminal disclaimer if necessary to secure issuance.

The third Action at page 4 takes the same position as discussed above in regard to the first obviousness-type double patenting rejection. Applicants therefore respectfully incorporate by reference all reasoning set forth above in response to the first obviousness-type double patenting rejection, with emphasis on claims 68 and 82 (and claim 69) and the definition of "antibody" in the specification, which is in accordance with its ordinary and customary meaning.

The second obviousness-type double patenting rejection is therefore overcome and should be withdrawn. Nonetheless, if double patenting rejection(s) are the only rejections remaining in the case, Applicants will overcome the rejection(s) by filing a terminal disclaimer.

VIII. Written Description Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4-9, 23-27, 41 and 49-83 are newly rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement in regard to the calcium flux inducing agents. Although Applicants respectfully traverse, the Action's concerns are overcome.

Claims 49-58, 60, 67, 76 and 77 are *prima facie* free from this rejection as specifically reciting an agent other than a calcium flux inducing agent.

The written description guidelines and case law in this area, as discussed in the third Action at pages 5-8, are understandably directed to the written description support for the novel features of a claimed invention. In contrast, the "calcium flux inducing agents" recited in the present claims are not the subject of the invention, but are recited for use in combination with anti-aminophospholipid antibodies, which the inventors surprisingly discovered to be effective for tumor vasculature targeting and tumor treatment. Thus, although the claimed invention concerns new and surprising combinations for targeting tumor vasculature and treating tumors, the calcium flux inducing agents subject to the written description rejection were well-known in the art prior to the present invention.

Applicants first respectfully point out that the present rejection is at odds with the first obviousness-type double patenting rejection in this case. As set forth above, the third Action rejects claims in this application as not being patentably distinct from claims 1-11, 17-20 and 27-54 in the '760 patent, claims 34, 51 and 52 of which are directed to combination treatment methods using anti-aminophospholipid conjugates and "calcium flux inducing agents". As claims 34, 51 and 52 in the '760 patent are patentable, and as the Office holds that the present claims are not patentably distinct from those issued claims, then the present claims must also be patentable, particularly as the '760 patent and the present application have the same priority date and describe calcium flux inducing agents in the same manner. Issuance of claims 34, 51 and 52 in the '760 patent, with the same claim language as currently rejected, thus supports a finding of patentability for the present claims.

In addition, calcium flux inducing agents were generally known in the art prior to the invention. For example, the role of increased intracellular calcium in apoptosis was well-known, including increases resulting from the influx of extracellular calcium and the release of calcium from mitochondrial and other intracellular stores. Thus, many agents that induce apoptosis were known to be calcium flux inducing agents.

Moreover, a number of therapeutic agents, including those used clinically to treat cancer, were known to be calcium flux inducing agents prior the invention. By way of example only, the following anti-cancer agents, each disclosed as a second therapeutic agent in the present specification, were all known to be calcium flux inducing agents prior the invention: cyclophosphamide (Al-Nasser, *Comparative Biochemistry & Physiology*, 121:209-214, 1998; **Exhibit A**); cisplatin (Campbell & Al-Nasser, *Toxicology*, 114(1):11-17, 1996; **Exhibit B**; see also, adriamycin reference attached to Exhibit B and discussed in Exhibit A); chlorambucil (Mentz *et al.*, Blood, 88(6):2172-82, 1996; **Exhibit C**); doxorubicin (Solem *et al.*, *Toxicology & Applied Pharmacology*, 129(2):214-22, 1994; Dodd *et al.*, *J. Clin. Invest.*, 91(4):1697-705, 1993; Kim *et al.*, *J. Mol. Cell. Cardiol.*, 21(5):433-6, 1989; **Exhibit D**); tumor necrosis factor-α (Bellomo *et al.*, Cancer Res., 52(5):1342-6, 1992; and Koller *et al.*, *Brain*, 119(6):2021-7, 1996; **Exhibit E**); and Vitamin D derivatives[1] (Vandewalle *et al.*, *Int. J. Cancer*, 61(6):806-11, 1995; **Exhibit F**).

As calcium flux inducing agents were well known in the art prior to the invention, the specification need not include significant details to satisfy the written description requirement for using such agents in the claimed combinations. An adequate written description need only

[1]Vitamin D derivatives are retinoids, see specification at Table C and Majewski *et al.*, "Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis," *J. Invest. Dermatol. Symp. Proc.*, 1(1):97-101, 1996, incorporated by reference into the specification.

convey with reasonable clarity to one skilled in art that, as of the filing date sought, the inventor was in possession of the invention as claimed. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111 (Fed. Cir. 1991). By describing the novel and non-obvious treatments of the invention in detail, and referring to their combination with known agents, including calcium flux inducing agents, the present specification satisfies the written description requirement.

Accordingly, the written description rejection is overcome and should be withdrawn. Nonetheless, and without acquiescing with the present rejection in any way, it will be noted that most claims no longer contain the term calcium flux inducing agent (or calcium ionophore), which is now confined to independent claim 73 and dependent claims 59 and 60.

The written description rejection is thus either overcome or moot, and should therefore be withdrawn.

IX. Enablement Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4, 5, 7-9, 23-27, 41 and 49-83 are also newly rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enabling support for antibodies other than anti-PS antibodies, and where the second therapeutic agent is H_2O_2, thrombin or a calcium flux inducing agent. Although Applicants respectfully traverse, the Action's concerns are overcome.

A. Antibodies to Aminophospholipids

The third Action at pages 8-12 alleges that the specification fails to enable the claimed combination treatment methods using an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, other than where the antibody binds to the aminophospholipid, phosphatidylserine (PS). The rejection is *prima facie* improper on various grounds.

The present specification teaches, "the prominent aminophospholipids found in mammalian biological systems are the negatively-charged phosphatidylserine ("PS") and the neutral or zwitterionic phosphatidylethanolamine ("PE"), which are therefore preferred aminophospholipids for targeting by the present invention" (specification at page 6, lines 27-30). The specification also teaches that the antibodies may bind to an aminophospholipid "complexed in a targetable form on the luminal surface of tumor vascular endothelial cells", such as in an aminophospholipid-protein complex, *e.g.*, a complex of phosphatidylserine and β_2-glycoprotein I (specification at page 7, lines 3-4 and 25-30).

According to established practice, the specification "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements". *In re Marzocchi & Horton*, 169 USPQ 367 (CCPA 1971), emphasis as in original. The third Action accepts that the specification is enabling for the use of antibodies that bind to PS, but not for antibodies that bind to PE or antibodies that bind to aminophospholipid-protein complexes. However, no pertinent reasoning is offered in support of such a position and the rejection is thus *prima facie* improper.

The third Action at page 10 alleges, "the specification appears to be silent on a correlation between the use of any antibody to any and/or all aminophospholipid and the treatment of a vascularized tumor; and further, the specification does not appear to suggest a nexus between the expression, accessibility and/or complexation of any other aminophospholipid on the luminal surface of tumor vascular endothelial cells". Applicants cannot understand how the Action could have reached such positions.

In contrast, the specification consistently explains that the two aminophospholipids, PS and PE, are normally segregated to the inner surface of the plasma membrane, and that the same

aminophospholipid translocase transports PE and PS (specification at page 49, lines 14-20, and Julien *et al.*, 1993, 1995, 1997, each incorporated by reference into the specification). The specification also teaches the inventors' discovery that PS and PE, and complexes thereof, become exposed on tumor vascular endothelial cells due to the same conditions and resulting from the same mechanisms, and can thus be successfully targeted in the same manner.

As PS and PE are highly related molecules, and the same tumor microenvironment results in their coincident exposure on tumor vascular endothelial cells, where they optionally form complexes with serum proteins, the specification provides a clear nexus between the demonstrated *in vivo* tumor vasculature targeting and tumor treatment using antibodies that bind to PS, and the same treatments using antibodies that bind to PE and aminophospholipid-protein complexes. Indeed, should the Office believe that the specification teaches that PE or aminophospholipid-protein complexes cannot be targeted in the same manner as PS, Applicants most respectfully request that the Office point out those portions of the specification believed to support such a position.

Although the third Action at pages 10-12 cites a number of references, they have no relevance to the Action's position that the specification enables tumor vasculature targeting and tumor treatment using antibodies that bind to PS, but not using antibodies that bind to PE or aminophospholipid-protein complexes on the luminal surface of blood vessels of a vascularized tumor. In particular, Jain, *Scientific American*, 271(1):58-65, 1994 ("Jain"), is cited for the position that there are barriers to the delivery of drugs into solid tumors. Applicants are perplexed that the third Action has cited Jain - - as the claimed invention overcomes all the drug delivery problems of Jain by discovering antibodies that bind to targets on the luminal surface of

blood vessels of a vascularized tumor (see also, specification at background, summary; following response to obviousness rejection).

Similarly, Dillman, *Annals of Internal Medicine*, 111:592-603, 1989 ("Dillman") and Weiner, Seminars in Oncology, 26(4):41-50, 1999 ("Weiner") refer to the problems of tumor cell heterogeneity and distribution/delivery, which are overcome by the present invention (again, see specification at background, summary). As to the possibility of HAMA (human anti-mouse antibody) responses mentioned in Dillman and Weiner, it will be noted that the generation of humanized antibodies is known in the art (see, *e.g.*, Devaux, cited in the third Action at page 16) and that the present specification enables humanized and fully human antibodies. In addition, two clinical trials using a chimeric (mouse-human) antibody in accordance with the present invention have already been approved by the FDA (see website of licensee, Peregrine Pharmaceuticals, Inc.), thus negating concerns over HAMA.

The third Action cites Ran *et al.*, *Cancer Res.*, 62:6132-40, 2002 ("Ran, 2002") at page 11, but does not explain why Ran, 2002 would support the position that tumor vasculature targeting and tumor treatment using antibodies that bind to PS are enabled, whereas such methods using antibodies that bind to PE or aminophospholipid-protein complexes are not enabled.

Finally, at pages 11-12 the third Action cites two pages from a cell culture manual from over 20 years ago ("Freshney") and a one page letter ("Dermer"), but again fails to explain why these pages support the position that tumor vasculature targeting and tumor treatment using antibodies that bind to PS are enabled, whereas such methods using antibodies that bind to PE or aminophospholipid-protein complexes are not enabled. In light of the successful use of antibodies that bind to PS to target tumor vasculature and treat tumors *in vivo*, and the structural

and functional correlations between PS and the closely related PE, and complexes of each that form following exposure on the tumor vasculature, the third Action has not set forth any meaningful reasons to doubt the objective teaching in the specification, which therefore *must* be taken as enabling. *Marzocchi & Horton, supra.*

In any event, even if sufficient reason to doubt the specification had been advanced, an enablement rejection "can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling." *Marzocchi & Horton, supra.* Thus, although the rejection is *prima facie* improper, and the burden has been improperly shifted to the Applicants, the following additional evidence is provided, which definitively overcomes the rejection.

Firstly, the present rejection is significantly in conflict with the earlier examination of this application and numerous issued U.S. patents. Notably, in the first Action, the present claims were rejected as not being patentably distinct from claims 4, 27-29, 42, 47 and 68 of the above-referenced '693 patent. The '693 patent claims methods of tumor vasculature targeting and tumor treatment using naked antibodies that bind to aminophospholipids, optionally in combination with a second anti-cancer agent. In reply to the double patenting rejection, Applicants submitted a Terminal Disclaimer. Thus, it is agreed that the present claims are not patentably distinct from the issued claims in the '693 patent.

The method claims issued in the '693 patent recite the use of an antibody, or antigen-binding fragment thereof, "that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor", *i.e.*, the phrase now subject to rejection. As the claims in the '693 patent are patentable, and as the Office holds that the present claims are not patentably distinct from the issued claims, then the present claims must also be patentable, particularly as the specifications and priority dates of the '693 patent and the present application are the same.

Issuance of the '693 patent, with the same claim language as currently rejected, and yet earlier determined to be patentable, thus compels a finding of patentability for the present claims. 35 U.S.C. § 282. See also:

> "When multiple patents derive from the same initial application, the prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation".
>
> *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813, 1816 (Fed. Cir. 2001).

The enablement rejection is also in conflict with the first and second obviousness-type double patenting rejections set forth above. The second and third Actions rejected claims in this application as not being patentably distinct from claims in the '760 patent and '694 patent, two patents directed to tumor vasculature targeting and tumor treatment using aminophospholipid-binding conjugates, optionally in combination with a second anti-cancer therapy ('760 patent). The method claims issued in the '760 and '694 patents recite the use of an aminophospholipid-binding conjugate in which the targeting agent "binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor", the phrase now subject to rejection. As the claims in the '760 and '694 patents are patentable, and as the Office holds that the present claims are not patentably distinct from those issued claims, then the present claims must also be patentable.

Additionally, the present rejection is clearly overcome by the following evidence. The use of antibodies that bind to PS is accepted as enabled. The specification teaches that PE becomes translocated to the surface of morphologically intact tumor vascular endothelial cells in the same manner as PS, and thus is a target for therapeutic intervention. This is clearly demonstrated in **Exhibit G** (Marconescu *et al.*, Presentation #1053, 97th AACR Annual Meeting, April 1-5, 2006, Washington, DC), which shows the coincident exposure of PE and PS

on the surface of irradiated endothelial cells. Note the conclusions that PS and PE are externalized together, appear simultaneously on the same cell surface regions and stay together during subsequent movement on the cell surface (**Exhibit G**). Thus, any doubts over the nexus between PS expression and accessibility and PE expression and accessibility are resolved.

The specification as filed already includes *in vivo* evidence of successful tumor vasculature targeting and tumor treatment using an aminophospholipid-binding conjugate that binds to both PS and PE. Specifically, Example XIII shows the anti-tumor effects resulting from the *in vivo* administration of an aminophospholipid-binding conjugate in which annexin V, which binds to both PS and PE (see Ran, 2002 cited by the third Action, *e.g.*, Ran, 2002 at page 6132, column 2; page 6153; Table 1), is linked to the coagulant, truncated Tissue Factor (tTF). The annexin V-tTF conjugate induced specific tumor blood vessel coagulation in HT29 tumor bearing mice (specification at Example XIII). Ran, 2002 extends the successful *in vivo* targeting data using annexin V (Ran, 2002, throughout).

Evidence of successful tumor vasculature targeting and tumor treatment using an aminophospholipid-binding construct that binds specifically to PE is shown in **Exhibit H** (He & Thorpe, Presentation #4561, 95th AACR Annual Meeting, March 27-31, 2004, Orlando, Florida). This study uses a duramycin-IgG conjugate, in which duramycin, which strictly recognizes PE, is linked to a non-targeting IgG to remove its hemolytic effect. Note that the coincident behavior of PE and PS in the tumor microenvironment, and their exposure on tumor vasculature due to stress conditions, is again documented. The duramycin-IgG localized to tumor endothelium in tumor-bearing mice, but not to blood vessels in normal tissues, and inhibited the growth of syngeneic tumors in the animals without toxicity (**Exhibit H**).

Thus, there can be no remaining doubts concerning *in vivo* targeting of both PS and PE (specification at Example XIII; Ran, 2002) or *in vivo* targeting specifically to PE on the tumor vasculature (**Exhibit H**).

The use of antibodies that bind to an aminophospholipid-protein complex on the luminal surface of blood vessels of a vascularized tumor is also enabled. The inventors have generated an antibody, 3G4, which binds to aminophospholipid-protein complexes, most particularly to a complex of PS and β_2-glycoprotein I (Ran *et al.*, *Clin. Cancer Res.*, 11:1551-1562, 2005; **Exhibit I**). The 3G4 antibody localizes to complexes of PS and serum proteins on the surface of vascular endothelial cells in tumors and exerts anti-tumor effects against several tumor types without toxicity (**Exhibit I**, throughout).

The 3G4 antibody has also been shown to function surprisingly well in combination therapies. For example, in combination with the chemotherapeutic agent, docetaxel, where the increased anti-tumor effect of the combination was statistically significant and was no more toxic than docetaxel alone (Huang *et al.*, *Cancer Res.*, 65(10):4408-4416, 2005; **Exhibit J**). Similarly, when used in combination with the chemotherapeutic agent gemcitabine, the 3G4 antibody strongly inhibited tumor growth and metastasis without contributing to toxicity (Beck *et al.*, *Int. J. Cancer*, 118:2639-2643, 2006; **Exhibit K**).

In vivo data in accordance with the original specification have thus been provided showing successful tumor vasculature localization and tumor treatment using antibodies and constructs targeting PS, both PS and PE, PE alone, and aminophospholipid-protein complexes, each present on the luminal surface of blood vessels of the vascularized tumor. Accordingly, this aspect of the enablement rejection, even though *prima facie* improper, is thus overcome and should be withdrawn.

B. Hydrogen Peroxide

Next, the third Action questions the enabling support for the use of H_2O_2 (hydrogen peroxide) as a second therapeutic agent (third Action at pages 12-13).

The third Action cites Jordan *et al.*, *J. Emergency Nursing*, 17(1):8-10, 1991 ("Jordan") in an attempt to back this aspect of the enablement rejection. The present claims are directed to administering "a therapeutically effective combination" of the claimed antibody and second therapeutic agent. Therefore, Jordan fails to support the rejection as Jordan concerns "intravenous injection of hydrogen peroxide", a "life-threatening" step (Jordan at page 10), which would not be seen as "a therapeutically effective combination" by one of ordinary skill in the art and which Jordan itself teaches against.

As with chemotherapeutic agents, which are lethal at high doses, it would be illogical to construe the present claims as reading on the life-threatening, intravenous injection of hydrogen peroxide, as that would be inoperative, and it is not the function of the claims to exclude every inoperative embodiment. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984). Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Accordingly, neither the claims, nor the specification, need to recite the life-threatening steps that are to be avoided, as such knowledge is well within the level of skill in the art.

However, one of ordinary skill in the art would understand that hydrogen peroxide can be used in cancer treatment under certain conditions, such as discussed in Symons, *Medical Hypotheses*, 57(1):56-58, 2001 ("Symons"), cited in the third Action, which teaches the "direct administration of aqueous H_2O_2 into solid tumours". Rather than supporting the rejection,

Symons thus strengthens Applicants' position that one of ordinary skill in the art would understand how to use H_2O_2 in the claimed combination treatments.

The third Action apparently believes Symons to be limiting, as the authors state that such uses of H_2O_2 would require "the development of systems/devices to deliver H_2O_2 to tumour tissue" (third Action at page 13). However, this in no way supports the enablement rejection, particularly as Symons immediately goes on to describe the properties of the delivery system envisioned (Symons at page 58, column 1). Moreover, the art of delivery systems for direct administration of agents into solid tumors is well developed. One need only search the U.S. patent literature to find dozens, if not hundreds, of patents concerning delivery and injection systems for use with solid tumors, including syringes, needles, catheters, and the like. In addition, prior to the present invention, devices were known for optimizing the infusion of drugs into solid tumors and for collecting drugs after tumor perfusion. See, *e.g.*, U.S. Patent No. 4,714,460 (**Exhibit L**).

Moreover, as described in Nicholson *et al.*, *Clinical Orthopaedics and Related Research*, 347:250-60, 1998 (**Exhibit M**), hydrogen peroxide had been used clinically as a chemical adjuvant for the removal of residual tumor cells for decades prior to the present invention (**Exhibit M** at Table 1, pages 250, 251 & 257, referring to Johnston *et al.*, Reference 19), and could likely be used successfully at even lower doses.

Therefore, this aspect of the enablement rejection is also overcome and should be withdrawn.

C. Thrombin and Calcium Flux Inducing Agents

The use of thrombin and calcium flux inducing agents as second therapeutic agents is included in the enablement rejection (third Action at page 8), although no reasoning is later

supplied to support these aspects of the rejection. Accordingly, as no reasons to doubt the specification have been advanced, the rejection is *prima facie* improper and should be withdrawn. *Marzocchi & Horton, supra.* Nonetheless, Applicants provide the following reasoning.

Regarding the combined use of anti-cancer drugs and blood coagulation factors, such as thrombin, to treat patients prior to the present invention, Applicants refer to U.S. Patent No. 4,536,387 (**Exhibit N**) and U.S. Patent No. 4,642,111 (**Exhibit O**), which teach methods of slowly releasing the drugs in the cancer tissue. Such methods could also be adapted for use with H_2O_2, as described above.

As to calcium flux inducing agents, as set forth above (**Section VIII**), calcium flux inducing agents include as examples a number of therapeutic agents used clinically to treat cancer prior the invention. These include, by way of example, cyclophosphamide, cisplatin, doxorubicin TNF-α and Vitamin D derivatives. As such agents are routinely used in the clinic, there can be no concerns regarding the enabling support for their combined use in the presently claimed invention.

Accordingly, these aspects of the enablement rejection are also overcome and should be withdrawn.

D. Conclusion

In light of the foregoing reasoning, the enablement rejection is overcome and should be withdrawn. Nonetheless, and without acquiescing with the present rejection in any way, it will be noted that most claims no longer contain the terms H_2O_2, thrombin, calcium flux inducing agent (or calcium ionophore), which are now confined to independent claim 73 and dependent claims 55, 56 59 and 60. Note also, that claim 73 is supplemented by claim 85, which

specifically recites that the second therapeutic agent is administered to the animal "via direct instillation into the vascularized tumor".

The enablement rejection is thus either moot or overcome, and should therefore be withdrawn.

X. First New Rejection Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, 49-54, 57, 58, 61-68 and 76-82 are newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman *et al.*, *Int. J. Oncol.*, 10:901-904, 1997 ("Fishman"), in view of Holash *et al.*, *Oncogene*, 18:5356-5362, 1999 ("Holash") and in combination with U.S. Patent No. 5,725,856 to Hudziak *et al.* ("Hudziak") or Hillman *et al.*, *Cell Immunol.*, 160:257-263, 1995 ("Hillman"). Although Applicants respectfully traverse, the Action's concerns are overcome.

In the first Action, Fishman was cited in a § 103(a) rejection in combination with Tschmelitsch. The rejection was overcome in light of Applicants' following reasoning: (1) Fishman does not teach or suggest the claimed invention, a combination treatment using a naked antibody to target an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor; (2) Tschmelitsch also fails to teach or suggest treatment by any targeting of blood vessels of a vascularized tumor and does not concern aminophospholipids; (3) Fishman and Tschmelitsch, even if combined, fail to teach or suggest the claimed invention; (4) Fishman and Tschmelitsch, both alone and in combination, teach away from the claimed invention; and (5) the invention works surprisingly effectively.

Fishman is now cited again, in combination with Holash, a post-filing date reference, and either Hudziak or Hillman. Fishman still has the same deficiencies. The citation of the critical post-filing date reference Holash is improper and the new § 103(a) rejection is thus *prima facie*

improper on legal grounds. The citation of Holash also fails on scientific grounds, as does the combination of Fishman and Holash, even if proper. Neither Hudziak nor Hillman has any teaching or suggestion relevant to the claimed invention. Thus, even if properly combined, including the post-filing date reference, Fishman, Holash and Hudziak or Hillman still fail to teach or suggest the claimed invention to one of ordinary skill in the art.

A. Fishman Provides No Relevant Teaching or Suggestion

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

The presently claimed invention is drawn to methods of treating an animal having a vascularized tumor by administering a therapeutically effective combination of at least a first antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor and at least a second therapeutic agent, as defined in the claims.

"Therapeutically effective" amounts and combinations, as defined in the specification, are amounts of naked or unconjugated anti-aminophospholipid antibodies that safely and effectively kill at least a portion of tumor vascular endothelial cells, promote coagulation in at least a portion of tumor blood vessels, occlude or destroy at least a portion of blood transporting vessels of the tumor, induce necrosis in at least a portion of a tumor, and/or induce tumor regression or remission (specification throughout, *e.g.*, pages 7-16, particularly page 12, lines 1-12). See also,

claims 72, 78 and 79. "Treating" tumors, as in the claimed invention, is thus distinguished from "anti-angiogenic therapies" which, although preventing micrometastasis, result only in tumor stasis when used alone (specification throughout, *e.g.*, page 16, lines 22-25; page 34, lines 1-2).

The third Action's discussion of Fishman (third Action at page 13) begins with a number of errors. The Action first cites Fishman as teaching the use of purified IgG anti-PS antibodies as an effective treatment for melanoma. However, as indicated in Fishman and by the next sentence of the third Action, Fishman does not actually teach "an effective treatment for melanoma", but only "an inhibitory effect on metastasis" (Fishman at page 903, column 1; third Action at page 13). Inhibition of metastasis, while useful in conjunction with an agent that exerts an anti-tumor effect, is not equivalent to, and does not teach or suggest, methods for treating tumors, as in the presently claimed invention.

This is made clear in the enclosed Declaration of Professor Adrian L. Harris ("Harris declaration")[2]. Although the Harris declaration concerns different claims and cited references, the central theme is highly pertinent to the present rejection, as the Harris declaration highlights important differences between inhibiting metastasis, which results from anti-angiogenic therapies, and tumor treatment by targeting and destroying tumor blood vessels, as in the claimed invention. It is explained that anti-angiogenic therapy is completely different from, and does not suggest, methods of treating tumors by targeting the established, vasculature of a solid tumour, which have many advantages (Harris declaration throughout, *e.g.*, paragraphs 6, 8, 11, 14 and 15). Professor Harris further explains that, as the established, blood-transporting vessels are the lifeline of the tumor, only targeting and destroying vessels, as in the present invention, could

[2]The Harris declaration was originally submitted in application Serial No. 08/205,330, now U.S. Patent No. 5,855,866 ("the '866 patent"; Attorney Docket Nos. 3999.000400, UTSD:393), and other applications by the present inventors and colleagues, and is currently made of record in the present application.

reasonably be expected to result in tumor necrosis and concomitant tumor destruction (Harris declaration throughout, *e.g.*, paragraphs 16 and 17).

Thus, Fishman does not teach or suggest treating tumors, as in the claimed invention, but at best concerns only inhibiting metastasis, a very different phenomenon.

As detailed in Applicants' first response, Fishman also fails to teach or suggest a combination treatment for tumors using an antibody that binds an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, as required by the claims. The third Action largely addresses this by citing the post-filing date reference, Holash. This is legally and scientifically improper, to which Applicants' detailed response is given below. Other than citing the post-filing date Holash reference, the third Action's only reply to this important issue is to comment on the absence of the word "targeting" from the claims (third Action at page 18).

"Targeting" aminophospholipids has always been a clear component of the invention according to the ordinary and customary meaning of the claims, and particularly when read in light of the specification. For example, starting with the 'Field of the Invention' at page 2 and continuing throughout, the specification explains that "the invention [thus] provides safe and effective methods and compositions for the specific targeting and destruction of tumor blood vessels and for the treatment of solid tumors" (specification throughout, *e.g.*, page 2, lines 14-16; see also, pages 4, 5, 6, 7, 8, 16, 21 and 22). Nonetheless, and without acquiescing with any rejection in any way, "targeting" aminophospholipids has now been emphasized in all but claim 82, and all corresponding obviousness rejections are overcome and should be withdrawn on this basis alone.

The third Action continues, "while Fishman et al. does not characterize the tumor as being vascularized, the claimed functional limitation would be an inherent property of the

referenced method because as evidenced by Holash et al., upon inoculation of rats with tumor cells, many tumors rapidly co-opt existing host vessels to form an initially well-vascularized tumor mass" (third Action at page 13). The third Action thus contends that it does not appear that the claim language [binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor] results in a manipulative difference in the method steps when compared to the prior art disclosure, citing *Bristol-Myers Squibb Company vs. Ben Venue Laboratories*, 58 USPQ2d 1508 (Fed. Cir., 2001).

There are important legal, procedural and scientific differences between the present analyses and the holding in *Bristol-Myers*. First, Fishman does not concern tumor treatment, but only inhibiting metastasis, which does not teach or suggest "treating" tumors as claimed (*e.g.*, Harris declaration). Second, the reference relied upon to show the alleged "inherent property" is a post-filing date reference that cannot, by its very nature, show that the claimed invention would be legally obvious to one of ordinary skill in the art at the time the invention was made (see below). Third, Holash does not support the third Action's position legally or scientifically (see below). Fourth, and irrespective of the above, the claimed methods are combination therapies, which therefore absolutely have a "manipulative difference" from the prior art disclosure. Fifth, *Bristol-Myers* concerns only inherent anticipation and expressly excludes a ruling regarding obviousness[3].

Thus, Fishman, even if properly combined with Holash, does not teach or suggest tumor treatment using an antibody that binds to an aminophospholipid on the luminal surface of blood

[3]Additional differences from the present case are that (1) the record of *Bristol-Myers* expressly indicated that performing the prior art [Kris] today would literally infringe the claims at issue; (2) admissions were made about the prior art during prosecution; and (3) the key claim language was found to be non-limiting because (i) it was in the preamble and (ii) it was a voluntary amendment after allowance.

vessels of a vascularized tumor, let alone a combination treatment including such an antibody, as in the claimed invention.

B. The Citation of Holash is Legally Improper

The claims are drawn to combination treatment methods using an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor and a defined second therapeutic agent. Fishman at best concerns only inhibiting metastasis, which does not teach or suggest the tumor treatment of the claimed invention (Harris declaration), and the rejection thus fails on this basis.

As to the important claimed feature that the antibody "binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor", Fishman does not even teach any therapeutic intervention relating to "a vascularized tumor" or any therapeutic intervention concerning any aspect of "tumor blood vessels". Fishman particularly fails to teach or suggest any therapy requiring an antibody binding to "an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor". These facts are acknowledged by the third Action at pages 13 and 18. However, the third Action cites the post-filing date reference, Holash, in an attempt to cure these deficiencies. The citation of a post-filing date reference in an attempt to supply critical information missing from a first-cited reference is legally improper and the rejection is thus *prima facie* improper and overcome.

Before addressing the scope and content of the prior art, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102. MPEP 2141.01 I, at MPEP page 2100-126, column 1. In terms of an obviousness rejection under 35 U.S.C. § 103(a), the prior art must teach or suggest the claimed invention to one of ordinary skill in the art at the time the invention was made. MPEP 2141.01 III, at MPEP page 2100-126, column 2. Holash, which

was published on September 20, 1999, is not prior art against the present invention, which has an effective filing date of July 13, 1998[4]. Accordingly, as Holash is not prior art, it cannot be combined with Fishman (or Hudziak or Hillman) and the present rejection is *prima facie* improper and overcome.

Although there are limited exceptions to the rule that the critical reference must pre-date the filing date, set forth at MPEP 2124 (MPEP page 2100-68, column 1), none of these exceptions apply to the citation of Holash in the present case. The only exceptions that could possibly apply to obviousness rejections are that the post-filing date reference shows (1) a "universal fact"; (2) the characteristics of a prior art product; or (3) the level of ordinary skill in the art at or around the time the invention was made. None of these factors apply in this case. Holash is not cited to show the characteristics of a prior art product or the level of ordinary skill in the art. Holash definitely does not show a universal fact (see more details below). All other exceptions set forth at MPEP 2124 concern rejections other than for obviousness, *i.e.*, undue experimentation, critical claim parameters, inaccuracy in the specification, inventions being inoperative or lacking utility or indefinite claims.

Thus, the citation of Holash does not meet any of the limited exceptions to the rule that the critical reference must pre-date the filing date. Therefore, even under this detailed analysis, the post-filing date Holash reference cannot be combined with Fishman (or Hudziak or Hillman) and the present rejection is improper and overcome.

The third Action's desire to combine Holash with Fishman concerns the attempt to show that certain claim limitations are "inherent". Namely, treating a "vascularized tumor" and using

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[4]The present application is a continuation of U.S. application Serial No. 09/351,543, filed July 12, 1999, now issued as U.S. Patent No. 6,406,693, which claims priority to second provisional application Serial No. 60/110,608, filed December 02, 1998, and to first provisional application Serial No. 60/092,672, filed July 13, 1998.

an antibody that "binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor". Such alleged inherencies are not, in fact, scientifically supportable (see more details below). In any event, the claimed invention is directed to combination treatments, and the Office has made absolutely no showing that the claimed combinations would be inherent in the prior art (also see more details below).

As to the third Action's focus on inherency, most of the case law regarding inherency is understandably limited to issues of inherent anticipation. The third Action has cited no authority for using a post-filing date reference in an attempt to show that one claimed embodiment was inherently disclosed in one of a combination of references cited under 35 U.S.C. § 103(a). In fact, the case law shows the reliance on an inherency argument as part of a § 103(a) rejection to be improper:

> "The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown".
>
> *In re Spormann and Heinke*, 150 USPQ 449, 452 (C.C.P.A. 1966).

Accordingly, even if antibody binding to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor "may be inherent in Fishman", this was not necessarily known. Therefore, and aside from the combination treatment aspect of the claimed invention, obviousness cannot be established as obviousness cannot be predicated on what is unknown. *In re Spormann, supra; In re Newell,* 13 USPQ2d 1248 (Fed. Cir., 1989).

The Federal Circuit has also made it clear that a successful inherency argument can only be established by showing that such "inherency would have been obvious to those skilled in the art when the invention was made". *Kloster Speedsteel AB vs. Crucible Inc.,* 230 USPQ2d 81 (Fed. Cir., 1986). This is clearly on point with Applicants' rebuttal against the present rejection.

Irrespective of what Holash may later show regarding inherency in Fishman, any obviousness rejection necessarily fails, as the post-filing date Holash reference (1999) simply cannot show the claimed invention to have been obvious to those skilled in the art when the invention was made (1988).

Moreover, the Federal Circuit extended the above holdings to establish that obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir., 1993). Therefore, even if antibody binding to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor was later "established to be inherent in Fishman", which is clearly not the case here, a *prima facie* case of obviousness still has not been established as obviousness cannot be predicated on what is not known at the time an invention is made, even if inherency is later established.

The third Action also extensively uses the teaching of the present specification in an attempt to support the inherency theories and the obviousness rejection (third Action at pages 18 and 19). Notably, "the specification discloses that phosphatydilserine [*sic*] is expressed in tumor blood vessels (Examples VIII page 163). Thus, in view of the specification, there does not appear to be any difference..." (third Action at page 19, emphasis added). By this improper use of hindsight, the third Action "falls victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983). Moreover, such analyses are also expressly prohibited when considering inherency. "An inventor's explanation of how the invention works does not render obvious that which is otherwise unobvious, for purposes of

patentability". If anything, the inventor's teaching supports the unobviousness of the discovery. *In re Glaug*, 283 F.3d 1335, 1342 (Fed. Cir. 2002).

Accordingly, the citation of Holash is *prima facie* improper as Holash is a post-filing date reference; and nothing in the case law concerning inherency rescues the citation of Holash. Therefore, the rejection based upon Fishman and Holash is improper and overcome, irrespective of the later improper combination with Hudziak or Hillman.

C. The Citation of Holash is Scientifically Flawed

The deficiencies of Fishman and the legally improper citation of the post-filing date Holash reference are detailed above. Applicants provide the following scientific reasoning to address any remaining concerns that the Office may have concerning the citation of Holash and possible inherency issues, and to definitively show that Fishman, even if properly combined with the post-filing date Holash reference, and with Hudziak or Hillman, still fails to teach or suggest the claimed invention to one of ordinary skill in the art.

A limited exception to the rule that the critical reference must pre-date the filing date is where the post-filing date reference shows a "universal fact or scientific truism". MPEP 2124 (MPEP page 2100-68, column 1). Importantly, any such universal fact or scientific truism must still have been obvious to those skilled in the art when the invention was made". *In re Spormann, supra; Kloster Speedsteel, supra.* The third Action appears to take the position that Holash shows the rapid formation of an initially well-vascularized tumor mass to be a universal fact or scientific truism, such that Fishman's method would inherently treat an animal having a vascularized tumor using an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor. Leaving aside that Fishman does not teach treating a tumor (see above), and that these analyses entirely ignore the claimed requirement for a second

therapeutic agent, Holash does not establish that any such universal fact or scientific truism existed, either at the time the invention was made or even afterwards.

First, Holash in its entirety is inconsistent with the third Action's attempts to show that tumor cells would have been understood to form an initially well-vascularized tumor mass at the time the present invention was made (third Action at page 13). In contrast, the 1999 Holash reference states, "it is widely accepted that most tumors and metastases originate as small avascular structures" (Holash at introduction) and thus describes its proposals as a "new model" (Holash at title). This new model challenges "the prevailing view that malignancies and metastases generally initiate as avascular masses that only belatedly induce vascular support" (Holash at abstract). Indeed, the "modification of the prevailing view" is acknowledged by third Action at page 18.

Thus, at about the time of the invention, before the 1999 Holash reference was published, those of ordinary skill in the art would have the same prevailing view, *i.e.*, that malignancies and metastases initiate as avascular masses that only belatedly induce vascular support. Accordingly, one of ordinary skill in the art would understand Fishman's "lung metastatic foci in mice inoculated with B-16 melanoma cells" to most likely be avascular masses. Clearly, the third Action has not cited the evidence required to show that, at the time of the invention, those of ordinary skill in the art would understand Fishman's lung metastatic foci to be well-vascularized tumor masses.

Indeed, the best that the third Action can offer is that Fishman's inoculation with B-16 melanoma cells "may" result in the formation of a vascularized tumor (third Action at page 18). Furthermore, Holash itself also teaches that, even with the new model, "there is widespread regression of these initially co-opted vessels, leading to a secondarily avascular tumor and

massive tumor loss" (Holash at discussion, emphasis added). Such uncertainties fall way below the standard needed to rely on inherency in a disclosure. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *Rijckaert* at 1957.

Second, there are many uncertainties in trying to extrapolate the observations of Holash to the experiment of Fishman, irrespective of whether this is considered at the time of Fishman, the present invention, Holash or the present time. For example, Holash states, "the relevance of our findings may well depend on the tumor in question" (Holash at discussion, emphasis added). As Fishman concerns only one type of tumor cell, one not used in Holash, there is no evidence to show that the B-16 melanoma cells of Fishman would grow as a well-vascularized tumor mass in the lung.

Holash continues to caution, "when tumor cells are introduced into a virtual or potential space, as is the case when tumors are deliberately implanted into the vitreous or subcutaneously, tumor cells do initially grow as space-filling avascular masses" (Holash at discussion, emphasis added). Although there are no specific details in Fishman, tumor cells are typically implanted subcutaneously in such studies, which casts further doubt on whether Fishman's B-16 melanoma cells grow as a well-vascularized tumor mass. Of particular relevance to melanoma, Holash teaches that tumors "deriving in the skin...may have to go undergo significant growth before they recruit vascular support" (Holash at discussion, emphasis added). Rather than just casting doubt on the formation of well-vascularized tumors, this indicates that, even if Fishman was viewed in the context of Holash, one of ordinary skill in the art would have no realistic basis to believe that either the initially inoculated B-16 melanoma cells or the lung metastatic foci would be a well-vascularized tumor mass, as alleged in the third Action.

Turning to other knowledge in the art before the invention was made, it was known both that melanoma cells form avascular tumors (*e.g.*, Alino & Hilario, *Exp. Cell Biol.*, 57(5):246-56, 1989; **Exhibit P**) and that other lung metastases can be avascular (Borgstrom *et al.*, *Anticancer Res.*, 15(3):719-28, 1995; **Exhibit Q**). Publications concerning avascular melanoma tumors (Elvira *et al.*, *Hepatology*, 37(3)674-85, 2003; Anurag *et al.*, *Microscopy Research & Technique*, 60(2):208-24, 2003; **Exhibit R**) and avascular lung metastases (Retsky *et al.*, *Breast Cancer Research & Treatment*, 65(3):217-24, 2001; **Exhibit S**) continued after the invention and to the present time.

The Federal Circuit has held that:

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."
>
> *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir 1999).

Accordingly, in light of all the uncertainties set forth above, tumor treatment using an antibody said to inherently bind an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor has not been established from Fishman, whether considered at the time the invention was made, or at the time of Holash. Therefore, the citation of the post-filing date Holash reference, even if proper, fails to support the rejection based upon Fishman and Holash, irrespective of the later improper combination with Hudziak or Hillman.

D. Fishman and Holash Still Fail to Teach or Suggest the Claimed Invention

The deficiencies of Fishman and the legally and scientifically improper citation of the post-filing date Holash reference are detailed above. In any event, the obviousness rejection over

Fishman, even if properly combined with Holash, and with Hudziak or Hillman, still fails to teach or suggest the claimed invention to one of ordinary skill in the art.

The presently claimed invention is a combination treatment method using an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor. Fishman does not concern treatment or targeting aminophospholipids on tumor blood vessels. The third Action agrees that Fishman does not teach any combination treatment (third Action at page 14). Holash, whilst commenting on anti-VEGF and angiopoietin-based therapies (Holash at discussion), does not teach targeting aminophospholipids on tumor blood vessels or any combination treatments.

Applicants' first response pointed out that Fishman is limited to strategies aimed at binding malignant and cancer cells, including "malignant melanoma cells" (Fishman throughout, *e.g.*, abstract, introduction, Table 1, Figure 1, Figure 3). The presently claimed methods are directed to targeting the blood vessels of vascularized tumors, which are normal cells. The third Action agrees with these facts (third Action at pages 18-19), but still maintains a § 103(a) rejection relying on Fishman. The third Action's bases for maintaining the rejection, as set forth at page 19, are all flawed.

The third Action first takes the erroneous position that Fishman must "explicitly omit" the limitation "binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor" for the invention to be patentable (third Action at page 19). There is no requirement of 35 U.S.C. § 103(a) for the cited prior art to explicitly disclaim a particular claimed feature. Rather, the prior art must teach or suggest the claimed invention to one of ordinary skill in the art at the time the invention was made and provide a reasonable expectation of success. This Fishman does not do.

Next at page 19, the third Action improperly relies on the teaching of the specification in an attempt to support the rejection. "The specification discloses that phosphatydilserine [*sic*] is expressed in tumor blood vessels (Examples VIII page 163). Thus, in view of the specification, there does not appear to be any difference..." (third Action at page 19, emphasis added). Such use of hindsight is improper, whether concerned with a straightforward obviousness rejection or one involving an inherency theory. *W.L. Gore Assoc., Inc., supra; In re Glaug, supra.* It is impermissible to use the claims as a frame and the prior-art references as a mosaic to piece together a facsimile of the claimed invention. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988).

The third Action then contends that there does not appear to be a patentable difference between the active steps of the pending claims and those taught by Fishman, nor a difference in the end result (third Action at page 19). These statements are in error for several important reasons. First, the presently claimed invention requires a combination therapy step, which is completely absent from Fishman. Second, Fishman at best concerns only inhibiting metastasis, which does not teach or suggest "treating" tumors as claimed, and cannot produce such an end result (*e.g.*, Harris declaration). Third, the Holash reference used to allegedly show inherency is a post-filing date reference, which thus that cannot establish obviousness at the time the invention was made. Fourth, Holash does not anyway support the inherency theory as Holash teaches too many variables in tumor vascularity, which variables are further documented in the art before the invention was made.

The third Action at page 19 then concludes with comments regarding "the product" of the prior art and "the claimed product". This is also not relevant as Applicants are not claiming a product, but a method. Moreover, Applicants have clearly met the burden required to show that

the presently claimed combination treatment methods are neither taught or suggested, nor inherently disclosed, in the cited art. All the Action's concerns are therefore overcome.

Therefore, Fishman, even if combined with the post-filing date Holash reference, and further combined with Hudziak or Hillman, still fails to support the rejection.

E. Fishman, Holash and the Art Teach Away from the Claimed Invention

In addition to failing to teach or suggest important embodiments of the claimed invention to those of ordinary skill in the art, the cited combination of references actually teaches away from the invention in important respects. In particular, Fishman teaches away from the claimed invention by consistently teaching that phosphatidylserine is not expressed at the surface of normal cells, whereas these are precisely the cells bound by the antibodies in the claimed methods.

For example, Fishman states "cancer cells differ from normal cells by the expression of phosphatidylserine (PS) on their outer membrane surface" (Fishman at abstract). In regard to normal cells, Fishman teaches "phosphatidylserine (PS) is localized exclusively in the inner leaflet of the cell membrane of normal cells" (Fishman in the legend to Figure 3; see also, abstract; page 903, column 1). Fishman continues, "the translocation of PS from the inner to the outer cell membrane is typical of tumor cells" (Fishman in the legend to Figure 3; text at page 903, column 1).

Thus, as the tumor vascular endothelial cells targeted by the presently claimed invention are normal cells, and as Fishman expressly and repeatedly teaches that phosphatidylserine is not expressed at the cell membrane of normal cells, but rather is "localized exclusively in the inner leaflet", Fishman clearly teaches away from the claimed invention. Such teaching away in the art

is clear evidence of patentability. *Mendenhall v. Astec Industries, Inc.*, 13 USPQ 2d 1913, 1939 (Tenn. 1988), *aff'd*, 13 USPQ 2d 1956 (Fed. Cir. 1989).

There is absolutely nothing in Holash, or in Hudziak or Hillman, to counteract this overt teaching away in the primary reference. The rejection is thus *prima facie* improper and should be withdrawn for this additional reason. The third Action discusses this at page 19, but presents no valid reasons for discounting this important line of evidence (see above).

Moreover, as pointed out in Applicants' first response, by concerning tumor cells, rather than tumor vasculature, Fishman is representative of the standard, but problematic prior art of tumor cell targeting, which is discussed in the background section of the present specification. For example, the specification teaches that both chemotherapeutics and immunotoxins against tumor cells are limited by tumor cell resistance, leading to antigen-negative or antigen-deficient tumor cells, which can survive and repopulate the tumor or lead to further metastases (specification at background). The poor accessibility of tumor cells is another limitation in therapies aimed at tumor cells. The specification teaches that the tumor mass is generally impermeable to molecules of the size of antibodies and immunotoxins, such that the physical diffusion distances and the interstitial pressure within the tumor are significant limitations to therapies aimed at tumor cells (specification at background).

Should the third Action not be persuaded by these details in the specification, it will be noted that this line of reasoning and that of the specification are the same as currently advanced by the third Action itself to show difficulties in tumor cell treatment. Notably, the third Action at pages 10-12 cites Jain, Dillman and Weiner to show that there are many, many drawbacks in attempting to deliver drugs to tumor cells. These impediments include non-uniform blood delivery to all areas of the tumor; hindered drug delivery and distribution due to increased blood

viscosity, high interstitial pressure and inadequate convection; and problems of tumor cell heterogeneity, shed or internalized targets (third Action at pages 10-12). Although none of these drawbacks apply to the presently claimed methods using antibodies that bind to targets on normal cells at the luminal surface of tumor blood vessels, they are representative of the many problems known in the art of tumor treatment prior to the present invention, and discussed in the specification (see also, Tschmelitsch, cited in the first Action).

The present inventors developed vascular targeting methods for tumor treatment, at least in part, to overcome the many drawbacks associated with drug delivery to cancer cells, including those enumerated by the third Action. "Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness." *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988).

Fishman, both alone and in combination with the post-filing date Holash reference, and further in combination with Hudziak or Hillman, does not teach or suggest any aspect of tumor vasculature targeting, let alone targeting an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, as required by the presently claimed invention. Rather, Fishman generally represents the problematic prior art of tumor cell targeting and, in the context of phosphatidylserine, Fishman *teaches away* from the claimed invention by teaching that phosphatidylserine is not expressed by normal cells.

Such teaching away in Fishman is not counteracted by anything in Holash, or in Hudziak or Hillman, and the rejection is thus improper and should be withdrawn.

F. Hudziak and Hillman Also Teach Away from the Claimed Invention

Although neither of the primary references teach or suggest tumor treatment using an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a

vascularized tumor or combination treatments, the third Action summarily moves on to the combination of Fishman and Holash with Hudziak or Hillman. However, neither Hudziak nor Hillman, even if properly combined with Fishman and Holash, cures the deficiencies of Fishman and Holash and the rejection is thus still improper. Moreover, Hudziak and Hillman further teach away from the invention.

The third Action cites Hudziak as teaching a method of inhibiting the growth of tumor cells that over-express a growth factor receptor by administering antibodies, either alone or in combination with other cytotoxic factors (third Action at page 14). In particular, the third Action cites Hudziak as teaching that a cytotoxic factor exerts a cytostatic and cytotoxic effect, and refers to exemplary chemotherapeutic drugs and an anti-angiogenic agent (third Action at page 14).

The third Action cites Hillman as teaching the administration of IL-4 to tumor-bearing mice, stating that Hillman discloses that IL-4 treatment reduced the number of lung metastases (third Action at page 14).

As a preliminary matter, rejected claim 52, in which the recited second therapeutic agent is angiostatin or endostatin, appears to be even further removed from this rejection, as neither Hudziak nor Hillman seem to teach or suggest the use of angiostatin or endostatin in combination with another agent. Should the Office disagree, Applicants most respectfully request that the Office point out those portions of either Hudziak or Hillman believed to support the rejection as applied to angiostatin or endostatin as a second therapeutic agent. Otherwise, any future rejection of claim 52 relying on any references not presently recited in the rejection would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

Overall, neither Hudziak nor Hillman teaches or suggests administering an anti-aminophospholipid antibody, either alone or in combination, to treat a vascularized tumor. Hudziak and Hillman particularly fail to teach or suggest administering an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, whether alone or in combination with a second anti-cancer agent. Hudziak and Hillman thus markedly fail to cure the deficiencies of Fishman and Holash. Furthermore, Hudziak and Hillman themselves teach away from the claimed invention.

Importantly, Hudziak is limited to methods of inhibiting the growth of tumor cells. Not only tumor cells, but tumor cells that over-express a growth factor receptor (Hudziak at abstract), particularly the HER2 receptor (Hudziak, claims). Hillman is also limited to methods of inhibiting metastases of particular tumor cells. The tumor cells in Hillman are from human renal cell carcinoma (RCC) tumor lines, specifically chosen because they express high-affinity IL-4 receptors (Hillman at page 257, column 2).

Aside from focusing on HER2 and RCC, respectively Hudziak and Hillman thus still represent the old and problematic field of tumor cell targeting. The many drawbacks of the tumor cell targeting field, including *e.g.*, poor drug delivery to tumor cells and survival of antigen-deficient tumor cells, are documented in the specification and the prior art (including that cited by the third Action) and are all overcome by the present invention.

There is nothing in Hudziak or Hillman to teach or suggest any aspect of targeting the blood vessels of a vascularized tumor, as in the presently claimed invention. Hudziak and Hillman, even in combination with Fishman and Holash, do not teach or suggest alternatives to tumor cell targeting, and particularly fail to teach or suggest targeting any component, let alone an aminophospholipid, expressed on the luminal surface of blood vessels of a vascularized

tumor. Fishman and Holash in combination with Hudziak or Hillman thus fail to raise a *prima facie* concern under § 103(a).

The third Action further alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat a vascularized tumor (third Action at page 14; emphasis added). However, this ignores the facts that neither Fishman nor Hillman teaches the treatment of a vascularized tumor, and that the presence of a vascularized tumor does not inherently result from the administration of tumor cells or the presence of lung metastases. Importantly, none of the references concern combination methods for treating vascularized tumors using an antibody that binds to a marker on the luminal surface of tumor blood vessels, let alone an antibody that binds to an aminophospholipid on the luminal surface of tumor blood vessels. The third Action is thus ignoring the claimed invention as a whole, which is improper in an obviousness analysis. *In re Wright*, 6 USPQ 2d 1959, 1962 (Fed. Cir. 1988).

The third Action continues to allege that it would have been obvious to combine the teachings of the references because each of the therapeutics have been individually taught in the prior art to be successful in treating cancer, citing *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) (third Action at page 14). This again glosses over the fact that Fishman does not provide a "treatment" as claimed, overlooks the flaws in the inherency argument, and significantly over-simplifies knowledge of tumor biology. Moreover, even if each of the therapeutics were taught to treat cancer in the prior art, this does not establish obviousness. "Applicant [Wright] agrees that he has combined old elements.....The patentability of such combinations is of an ancient authority. Virtually all inventions are 'combinations', and *every* invention is formed of 'old

elements'....Only God works from nothing. Man must work with old elements". *In re Wright, supra.*

In any event, therapeutic benefits derived from binding tumor vasculature do not "flow logically" from references concerning tumor cells therapies or anti-angiogenic therapies, as these three areas have achieved a separate status in the art (*e.g.*, see Harris declaration). Although discussed mainly in contrast to anti-angiogenic therapies, Professor Harris also distinguishes therapies directed against tumor vasculature, as in the claimed invention, from those aimed at tumor cells, as in Hudziak and Hillman. Art confined to the old attempts to target and control neoplastic tumor cells, with all the attendant limitations, does not teach or suggest the innovative targeting of the normal tumor vascular endothelial cells, as in the present invention.

The third Action at page 17 also takes the curious position that it is not necessary for the Action to address Applicants' reasoning regarding the deficiencies of any reference other than Fishman. As Fishman admittedly fails to teach or suggest combination therapies (third Action at page 14), and as Hudziak or Hillman are the only references now cited to allegedly teach combination therapies, it is interesting that the Action chooses not to address such references. The citation of *Kerkhoven* does not support the Action's reasoning, as the third Action has improperly over-simplified tumor biology and as evidence is of record showing that Fishman (with Holash), Hudziak and Hillman do not flow logically together with the claimed invention, but rather concern therapies that have achieved a separate status in the art.

In addition, evidence of the surprising effectiveness of a combination therapy of the invention is already of record, demonstrating that tumor treatment using an antibody that binds to an aminophospholipid on the luminal surface of tumor blood vessels and the chemotherapeutic drug, docetaxel, produce synergistic effects (see Exhibit B to Applicants' first response).

The § 103(a) rejection is thus *prima facie* improper on various grounds, including the many deficiencies of Fishman and Hillman, none of which are cured by Hudziak or Hillman. In particular, none of Fishman, Holash, Hudziak or Hillman teach or suggest tumor treatment using an antibody to bind to tumor blood vessels, let alone tumor treatment using an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, or combinations of such treatments, and the art further teaches away from the claimed invention. The § 103(a) rejection is thus improper and should be withdrawn.

G. § 103(a) Conclusion

In light of the foregoing reasoning, the first new § 103(a) rejection is overcome and should be withdrawn. Nonetheless, and without acquiescing with the present rejection in any way, it will be noted that most claims no longer rely solely on an antibody that "binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor", which is now confined to independent claim 82 and dependent claims 86 and 87. Rather, most claims now recite that the antibody "targets and" binds to an "aminophospholipid-protein complex" on the luminal surface of blood vessels of the vascularized tumor. This language even further distances the claimed invention from the cited prior art, by further addressing specific concerns in the third Action ("targeting", as discussed in the third Action at page 18) and by further removing the claimed invention from Fishman and Holash.

Notably, neither Fishman nor Holash teach or suggest that an aminophospholipid-protein complex could be presented in a targetable form on the luminal surface of tumor vascular endothelial cells, and could thus serve as a specific marker for tumor vascular targeting and tumor treatment. Such observations are even more tightly confined to the present specification alone, and cannot be gleaned from the cited prior art, even considering Fishman and Holash

together. This language is particularly far removed from any suggestions in Fishman that PS may be exposed on malignant cancer cells. Aminophospholipid-protein complexes may be targeted by the invention because the aminophospholipids newly-exposed on the tumor vascular endothelial cells combine, in this membranous environment, with serum proteins, thereby forming aminophospholipid-protein complexes (*e.g.*, specification at page 7). As only the luminal surfaces of the tumor vascular endothelial cells are exposed to the blood, and not the surfaces of the malignant tumor cells, only the aminophospholipids exposed on tumor vascular endothelial cells can combine with serum proteins to form a targetable complex. Accordingly, most claims are even further patentable over the cited art.

Claims 72, 78 and 79 are even further distanced from the cited prior art. These claims particularly address specific concerns in the third Action by use of the terms "tumor-destructive amount", "tumor necrosis-inducing amount" and "amount effective to destroy or occlude at least a portion of the tumor blood vessels", respectively, which each overcome the Action's concerns regarding targeting and treatment (third Action at page 18). These claims are thus even further removed from any anti-angiogenic suggestions in Fishman.

The first new § 103(a) rejection is thus either moot or overcome, and should therefore be withdrawn.

XI. Second New Rejection Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, 49-54, 57, 58, 61-68 and 76-**83** are also newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Fishman and Holash references in further view of Campbell, Monoclonal Antibody Technology, pgs. 1-33, 1986 ("Campbell"). Although Applicants respectfully traverse, the Action's concerns are overcome.

The presently claimed invention is a combination therapy. However, no references alleged to show combination therapy have been cited; the rejection relying on just Fishman, the post-filing date reference Holash, and Campbell[5]. Accordingly, any future rejection of claim 83 relying on any references not presently recited in the rejection would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

In addition, even if Hudziak or Hillman were cited, the rejection of claim 52, in which the recited second therapeutic agent is angiostatin or endostatin, appears to be *prima facie* improper, as neither Hudziak nor Hillman seem to teach or suggest the use of angiostatin or endostatin in combination with another agent.

Campbell is cited for teaching an advantage of monoclonal antibodies over so-called "conventional antiserum" (third Action at page 15).

Aside from the foregoing issues, the rejection is improper on various grounds, including the many deficiencies of Fishman and Hillman, which are not cured by Hudziak or Hillman, and which the new citation of Campbell also fails to rectify. In particular, none of Fishman, Holash, Hudziak or Hillman, even if combined with Campbell, teach or suggest tumor treatment using an antibody to bind to tumor blood vessels, let alone tumor treatment using a monoclonal antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, or combinations of such treatments. In contrast, the art teaches away from the claimed invention.

[5]Note that neither Hudziak nor Hillman, cited in the first rejection under 35 U.S.C. § 103(a), have been cited as part of the present combination.

Certain claims also further distinguish over the cited combination, even including Campbell, for various additional reasons, as set forth above.

The second new § 103(a) rejection is thus either moot or overcome, and should therefore be withdrawn.

XII. Third New Rejection Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, **9**, 49-54, 57, 58, 61-68, **71** and 76-82 are also newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Fishman and Holash references in further view of U.S. Patent No. 6,824,780 to Devaux *et al.* ("Devaux"). Although Applicants respectfully traverse, the Action's concerns are overcome.

As set forth above, the presently claimed invention is a combination therapy. However, no references alleged to show combination therapy have been cited; the rejection relying on just Fishman, the post-filing date reference Holash, and Devaux[6]. Accordingly, any future rejection of claims 9 and/or 71 relying on any references not presently recited in the rejection would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

In addition, even if Hudziak or Hillman were cited, the rejection of claim 52, in which the recited second therapeutic agent is angiostatin or endostatin, appears to be *prima facie* improper, as neither Hudziak nor Hillman seem to teach or suggest the use of angiostatin or endostatin in combination with another agent.

Devaux is cited for teaching the generation of humanized antibodies, said to reduce immunogenicity and HAMA responses (third Action at page 16).

Importantly, Devaux is not available as prior art against the present invention, rendering this third § 103(a) rejection entirely improper. In particular, Devaux is a U.S. patent that issued

on November 30, 2004, based on an application filed October 27, 2000, which claims priority to two provisional applications, the earliest of which was filed October 29, 1999. Without even considering whether Devaux's claims for priority are proper, Devaux is not prior art against the present invention as the earliest possible date of Devaux (October 29, 1999) is after the July 13, 1998 effective filing date of the present application (note also, the July 12, 1999 filing date for the parent, '693 patent[4]).

This is another reason that any future rejection of claims 9 and/or 71 relying on any reference not presently recited in the rejection would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

Aside from the foregoing issues, and even if Devaux was available as prior art, the rejection is improper on various grounds, including the many deficiencies of Fishman and Hillman, which are not cured by Hudziak or Hillman, and which the new citation of Devaux also fails to rectify. In particular, none of Fishman, Holash, Hudziak or Hillman, even if combined with Devaux, teach or suggest tumor treatment using an antibody to bind to tumor blood vessels, let alone tumor treatment using a humanized antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, or combinations of such treatments. In contrast, the art teaches away from the claimed invention.

Certain claims also further distinguish over the cited combination, even including Devaux, for various additional reasons, as set forth above.

The third new § 103(a) rejection is thus either moot or overcome, and should therefore be withdrawn.

XIII. Fourth New Rejection Under 35 U.S.C. § 103(a)

Finally, claims 4, 6-**8**, 49-54, 57, 58, 61-68, **70** and 76-**83** are further newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Fishman and Holash references in further view of U.S. Patent No. 4,837,003 to Nicolotti ("Nicolotti"). Although Applicants respectfully traverse, the Action's concerns are overcome.

The presently claimed invention is a combination therapy. However, no references alleged to show combination therapy have been cited; the rejection relying on just Fishman, the post-filing date reference Holash, and Nicolotti[6]. Accordingly, any future rejection of claims 8, 70 and/or 83 relying on any references not presently recited in the rejection would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

In addition, even if Hudziak or Hillman were cited, the rejection of claim 52, in which the recited second therapeutic agent is angiostatin or endostatin, appears to be *prima facie* improper, as neither Hudziak nor Hillman seem to teach or suggest the use of angiostatin or endostatin in combination with another agent.

Nicolotti is cited for teaching that antibody fragments, rather than whole antibodies, are better suited for *in vivo* use (third Action at page 16). However, as taught in the present specification, and in contrast to Nicolotti, antibody fragments may not always be better suited for *in vivo* use than whole antibodies in the context of the present invention. For example, the specification teaches that anti-aminophospholipid antibodies for use in inducing complement-mediated lysis will generally include the Fc portion of the antibody (specification at page 14).

Aside from the foregoing issues, the rejection is improper on various grounds, including the many deficiencies of Fishman and Hillman, which are not cured by Hudziak or Hillman, and

which the new citation of Nicolotti also fails to rectify. In particular, none of Fishman, Holash, Hudziak or Hillman, even if combined with Nicolotti, teach or suggest tumor treatment using an antibody to bind to tumor blood vessels, let alone tumor treatment using an antibody fragment that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, or combinations of such treatments. In contrast, the art teaches away from the claimed invention.

Certain claims also further distinguish over the cited combination, even including Nicolotti, for various additional reasons, as set forth above.

The fourth new § 103(a) rejection is thus either moot or overcome, and should therefore be withdrawn.

XIV. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and accompanying documents, the present claims are in condition for allowance. Should Examiner Fetterolf have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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